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TETRAHEDRON LETTERS

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A straightforward synthesis of 4-substituted 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides

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Substituted 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides **11** have been efficiently prepared in steps from the suphamide **9** by condensation of anion **II**, derived from **9** by metal–halogen exchange, aromatic and aliphatic aldehydes and cyclodehydration of the so-formed alcohols **10** under acidic .itions. © 2000 Elsevier Science Ltd. All rights reserved.

'ords: bicyclic heterocyclic compounds; benzothiazines; lithiation; cyclization.

:eterocycles incorporating a sulfamido moiety have been reported to possess a variety of resting biological activities.[1] For example, aminothiadiazole 1,1-dioxides have shown antihyensive and vasodilating properties.[2] Sedative and mild tranquilizer behaviors have also been ›rted for benzothiadiazine dioxides.[3] Special mention should be made of bentazone (3-isopyl-1*H*-2,1,3-benzothiadiazin-4-one 2,2-dioxide) which presents an important herbicidal vity [4]

'he ual procedure for the preparation of fused 1*H*-2,1,3-thiadiazine 2,2-dioxides is a -step approach involving sulfamoylation of *ortho* substituted amino derivatives **1** followed by ; closure.[1] Thus, from *o*-aminobenzoates, *o*-aminobenzonitriles or 2-aminobenzophenones *H*)-oxo,[5] 4-amino[6] or 4-phenyl[7] 1*H*-2,1,3-benzothiadiazines **3** or **4** have been obtained ›ectively (Scheme 1).

:atalytic hydrogenation of **4** (X = Ph, CH_3), using Adams catalyst, yielded the corresponding -dihydro derivatives **5**. These compounds can be prepared directly by reaction of 2-aminobenımines **6** (X = H) with either sulfuryl chloride[8] or sulfamide.[9] More recently, Pews reported synthesis of 3-alkyl derivatives **7** by reaction of *N*-alkyl-*N'*-arylsufamides **2** (G = H) with ›xane.[10] The scope of these methods is related to the substitution in the benzo moiety and so C4 position was unsubstituted in almost all cases.

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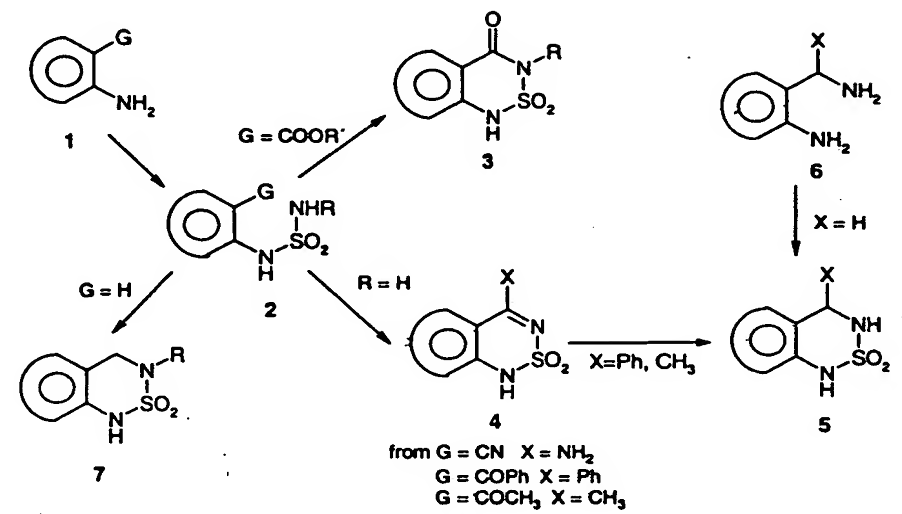


Scheme 1.

As 4-substituted 1*H*-2,1,3-benzothiadiazine 2,2-dioxides **11** were required for new drug candidate synthesis, we decided to explore a more straightforward synthetic approach. A simple retrosynthetic analysis led us to recognize that *o*-iodoaniline **8** could be a suitable precursor (Fig. 1). So we decided to explore this approach by carrying out, as the key step, the condensation of the corresponding ArLi derived from **9** with aldehydes in order to get alcohols **10**, which could subsequently be cyclodehydrated under acidic conditions.

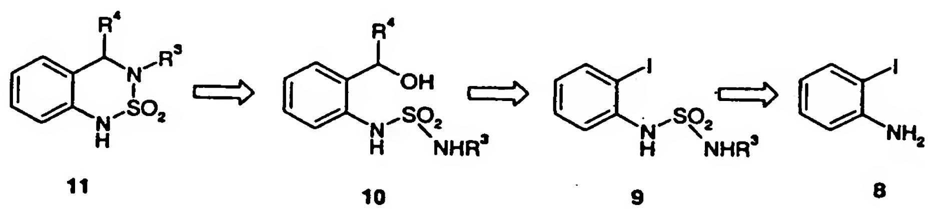
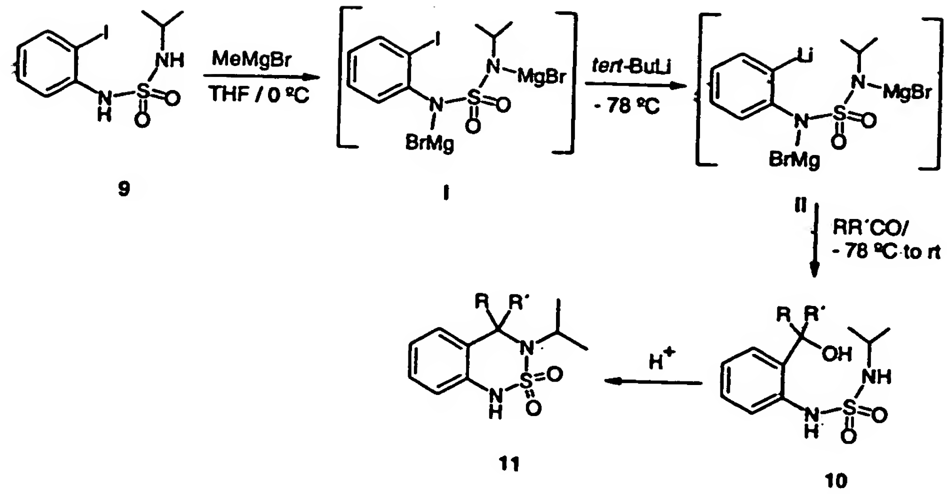


Figure 1.

In this communication, we report the successful transformation of **9** ($R^3 = i$-Pr, obtained from **8** by a standard procedure[10]) into **11**[11] via this approach, thus allowing different substitution patterns at C-4.

The synthesis of **10** required the formation of the trianion **II**, necessitating the removal of the two acidic protons of **9** before the metal–halogen exchange. For this purpose, we chose methylmagnesium bromide, a base which would not interfere with the halogen. The deprotonation was performed at 0°C in THF until no further methane evolution was observed. For the metal–halogen exchange, *tert*-BuLi was the reagent of choice due to its high iodine affinity, even in the presence of sensitive groups.[12] The process took place at −78°C over 20 min. Finally, the addition of the electrophile gave the desired alcohol **10** (Scheme 2).

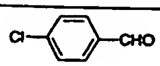
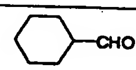
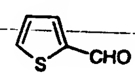
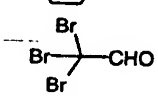
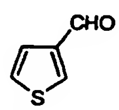
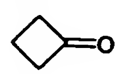
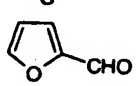
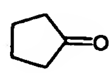
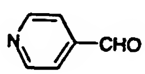
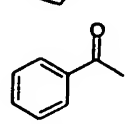
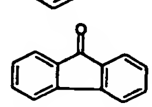
The condensation of **II** with aromatic and aliphatic aldehydes worked well (Table 1, entries a–g) giving **10** in good yields. The only exception was aldehyde of entry h, where the tribromoac



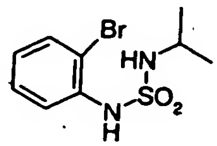
Scheme 2.

:hyde acted as a bromine donor, affording **12** (Fig. 2) in 70%. However, when ketones were ıs electrophiles (entries j–l) the condensation did not proceed, with only reduced product ig. 2) being isolated in more than 80%. In order to increase the reactivity of the ketones, BF_3 was added to the reaction but this only yielded a complex mixture of products.

Table 1
Two-step synthesis of 4-substituted 3,4-dihydro-*1H*-2,1,3-benzothiadiazine 2,2-dioxides **11**

Entry	RR´CO	Yield (%) 10	11	Entry	RR´CO	Yield (%) 10	11
a		80	82[a]	g		90	—
b		88	80[b]	h		—	
		80	80[b]	i		73	98[a]
d		86	24[b] (70)[c]	j		—	
e		62	97[a]	k		—	
f	$CH_3(CH_2)_8CHO$	77	67[a]	l		—	

[a] CH_3SO_3H/CH_2Cl_2/1h/rt (except for entry e as indicated in the text). [b] CF_3CO_2H /CH_2Cl_2/10 min./rt. [c] Saturated ethereal solution of hydrogen chloride/CH_2Cl_2)/10 min./-30° C.



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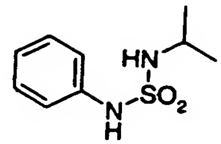

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Figure 2.

The one exception was cyclobutanone (entry i), which condensed quite well to yield the expected alcohol **10i** in 73% yield. These results can be explained by the facile enolization of both cyclopentanone and acetophenone when **II** is present, while the enolate of cyclobutanone possesses high skeletal strain and so is less readily formed. In this case the enolization is not thermodynamically favored and so the reaction with **II** can occur. Furthermore, the driving force of the condensation in this case could be associated with a release of strain when cyclobutanone reacts with **II**.

The final step was the acid-catalyzed cyclodehydration of the benzylic alcohols **10**. Methanesulfonic acid was initially used, producing the expected heterocycle **11** in high yield. However, 4-pyridine carbaldehyde required more vigorous conditions (reflux temperature), probably due to the protonation of the basic nitrogen atom. For the five-membered heterocyclic aldehydes (Table 1, entries b–d), trifluoroacetic acid, a weaker acid, was used yielding the expected products in good yields in the case of the thiophene carbaldehydes and a very poor yield (24%) for the furyl derivative. The sensitivity of the furan ring toward acid media required the cyclization of **10d** to be run at low temperature (–30°C, saturated ethereal solution of hydrogen chloride) in order to obtain a reasonable (70%) yield of **11d**. Finally, in the case of alcohols **10** derived from aliphatic aldehydes (Table 1, entries f and g), the dehydration to the corresponding alkene was a competing process, this being the sole isolated product in the case of **10g** (70%), while **11f** was isolated in 67% yield, with only a 15% yield of the alkene side product.

Representative experimental procedure:

Compound **10**: To a solution of the iodo derivative **9** (1.0 g, 2.94 mmol) in dry THF (30 mL) stirred at 0°C was added a 3 M solution of methyl magnesium bromide (2.15 mL, 6.47 mmol). The mixture was stirred for 1 h and then cooled to –78°C. A 1.7 M solution of *tert*-BuLi (3.8 mL, 6.47 mmol) was added and the solution stirred at this temperature for 30 min, then the carbonyl derivative (1.2 mol) was added at –78°C. The mixture was then heated to room temperature. After 1 h at this temperature, the reaction mixture was quenched with saturated ammonium chloride solution and extracted into CH_2Cl_2 (3×25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by flash chromatography using hexane/EtOAc (8:2) as eluent.

Compound **11**: To a solution of the benzylic alcohol **10** (1 mmol) in CH_2Cl_2 (15 mL) was added the corresponding acid (5 mmol) and the mixture was stirred as described for each case (see footnotes to Table 1). The reaction mixture was quenched with saturated $NaHCO_3$ solution and worked-up as indicated above for **10**. The crude mixture was purified by flash chromatography using hexane/EtOAc (8:2) as eluent. The oily product obtained crystallized as a white powder on standing with hexane.

Acknowledgements

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